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**Novel Vaginal Ring Design for the Controlled
Release of the Macromolecule Microbicide 5P12-
RANTES**

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Background: 5P12-RANTES, a chemokine analogue that potently blocks the HIV CCR5 coreceptor, is being developed as both a vaginal and rectal microbicide for prevention of sexual transmission of HIV. Development of low-cost intravaginal rings (IVRs) for controlled release of such protein molecules is significantly more challenging than for small-molecule antiretrovirals due to poor permeability. Here, we report a new reservoir-type IVR design comprising a drug-loaded/hydropropyl methylcellulose (HPMC) core and a non-medicated sheath with orifices for controlled release 5P12-RANTES.

Methods: Silicone elastomer IVRs containing model drug lysozyme or experimental drug 5P12-RANTES were manufactured via injection molding. HPMC particle size, HPMC molecular weight and HPMC loading, and number of orifices were varied across the IVR formulations. In vitro release testing was performed and 5P12-RANTES quantified using ELISA and HPLC-UV. Fluid ingress into the IVRs was assessed by weight increase and uptake of methylene blue.

Results: Using custom molds, the novel IVRs were easy to manufacture. Preliminary results with lysozyme revealed that a greater HPMC loading, molecular weight, and particle size correlated with a greater drug release rate and degree of swelling. Adjusting core surface area exposure, by increasing orifice size/number, correlated with greater swelling and 5P12-RANTES release (9.34 mm² surface area exposure, 3.5 ± 1.9 µg/day; 56.04 mm², 8.9 ± 1.8 µg/day; 210.90 mm², 39.3 ± 19.7 µg/day).

Conclusions: The ring design provided controlled release of 5P12-RANTES, and could be applied to a broader range of large molecule actives. This research supports continued development of the 5P12-RANTES IVR. Sheep pharmacokinetics studies are currently being conducted.